Evidence Report

Chapter 1. Introduction

This evidence report by the University of Ottawa's Evidence-Based Practice Center (EPC) concerning the health effects of omega-3 fatty acids on asthma is one among several that address topics related to omega-3 fatty acids that were requested and funded by the Office of Dietary Supplements, National Institutes of Health (NIH), through the EPC program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-New England Medical Center (Tufts-NEMC) EPC, the Southern California/RAND (SC-RAND) EPC, and the University of Ottawa EPC (UO-EPC)—each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of these reports is to summarize the current evidence concerning the health effects of omega-3 fatty acids on the following: cardiovascular diseases, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, autoimmune diseases, immune-mediated diseases, transplantation, mental health, and, neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

The focus of this report is on asthma outcomes in humans. In this chapter, the metabolism, physiological functions, and sources of omega-3 fatty acids are briefly discussed. This constitutes background material, putting in context the data presented in the evidence report. As well, the description of the U.S. population intake of omega-3 fatty acids is provided in response to a general question posed within the task order. This introductory material is then complemented by a brief review of the epidemiology and natural history of asthma, in addition to its treatment. Subsequent chapters describe the methods used to identify and review studies related to omega-3 fatty acids and asthma, findings related to the effects of omega-3 fatty acids on asthma, and recommendations for future research in this area.

Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. It encompasses saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. Unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Polyunsaturated fatty acids (or PUFAs) can be classified, on the basis of their chemical structure, into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The omega-3 or *n-3* notation means that the first double bond in this family of PUFAs is 3 carbons from the methyl end of the molecule. The same principle applies to the omega-6 or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (i.e., 9 kcal/g or 37 kJ/g).

Of all fats found in food, two—alpha-linolenic acid (chemical abbreviation: ALA; 18:3 n-3) and linoleic acid (LA; 18:2 n-6)—cannot be synthesized in the human body, yet these are necessary for proper physiological functioning. These two fats are thus called "essential fatty acids." The essential fatty acids can be converted in the liver to long-chain polyunsaturated fatty

acids (LC PUFAs), which have a higher number of carbon atoms and double bonds. These LC PUFAs retain the omega type (n-3 or n-6) of the parent essential fatty acids.

ALA and LA comprise the bulk of the total PUFAs consumed in a typical North American diet. Typically, LA comprises 89% of the total PUFAs consumed, while ALA comprises 9%. Smaller amounts of other PUFAs make up the remainder.[1] Both ALA and LA are present in a variety of foods. For example, LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA, which is consumed in smaller quantities, is present in leafy green vegetables and in some commonly used oils, including canola and soybean oil. Some novelty oils, such as flaxseed oil, contain relatively high concentrations of ALA, but these oils are not commonly found in the food supply.

The Institute of Medicine (IOM) suggests that, for adults 19 and older, an adequate intake (AI) of ALA is 1.1-1.6 grams/day, and 11-17 grams/day for LA.[2] Recommendations regarding AI differ by age and gender groups, and for special conditions such as pregnancy and lactation.

As shown in Figure 1, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3) can act as competitors for the same metabolic pathways as arachidonic acid (AA; 20:4 n-6). In human studies, the analyses of fatty-acid compositions in both blood phospholipids and adipose tissue have shown a similar competitive relationship between omega-3 LC PUFAs and AA. General scientific agreement supports an increased consumption of omega-3 fatty acids and reduced intake of omega-6 fatty acids to promote good health. However, for omega-3 fatty acid intake, the specific quantitative recommendations vary widely among countries not only in terms of different units — ratio, grams, total energy intake — but also in quantity.[3] Furthermore, there remain numerous questions relating to the inherent complexities concerning omega-3 and omega-6 fatty acid metabolism, in particular the relationships between the two fatty acids. For example, it remains unclear to what extent ALA is converted to EPA and DHA in humans, and to what extent the high intake of omega-6 fatty acids compromises any benefits of omega-3 fatty acid consumption. Without the resolution of these two fundamental questions, it remains difficult to study the importance of the omega-6/omega-3 fatty acid ratio.

Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids share the same pools of enzymes and go through the same oxidation pathways while being metabolized (Figure 1). Once ingested, the parent of the omega-3 fatty acids, ALA, and the parent of the omega-6 fatty acids, LA, can be elongated and desaturated into LC PUFAs. LA is converted into gamma-linolenic acid (GLA; 18:3 n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the long-chain omega-6 fatty acid, AA, while ALA can be converted, to a lesser extent, to the long-chain omega-3 fatty acids, EPA and DHA. However, the conversion from parent fatty acids into LC PUFAs occurs slowly in humans, and conversion rates are not well understood. Because of the slow rate of conversion, and the importance of LC PUFAs to many physiological processes, humans must augment their level of LC PUFAs by consuming foods rich in these important compounds. Meat is the primary food source of AA, and fish is the primary food source of EPA.

The specific biological functions of fatty acids depend on the number and position of double bonds and the length of the acyl chain. Both EPA and AA are 20-carbon fatty acids and are precursors for the formation of prostaglandins (PGs), thromboxane (Tx), and leukotrienes

(LTs)—hormone-like agents that are members of a larger family of substances called eicosanoids. Eicosanoids are localized tissue hormones that seem to be one of the fundamental regulatory classes of molecule in most higher forms of life. They do not travel in the blood, but are created in the cells to regulate a large number of processes, including the movement of calcium and other substances into and out of cells, dilation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and, the control of fertility, cell division, and growth.[4]

As shown in Figure 1, the long-chain omega-6 fatty acid, AA, is the precursor of a group of eicosanoids including series-2 prostaglandins (PG_2) and series-4 leukotrienes (LT_4). The omega-3 fatty acid, EPA, is the precursor to a group of eicosanoids including series-3 prostaglandins (PG_3) and series-5 leukotrienes (LT_5). The series-2 prostaglandins and series-4 leukotrienes derived from AA are involved in intense actions (such as accelerating platelet aggregation, and enhancing vasoconstriction and the synthesis of mediators of inflammation) in response to physiological stressors. The series-3 prostaglandins and series-5 leukotrienes derived from EPA are less physiologically potent than those derived from AA. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate excessive series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins, which are derived from the omega-3 fatty acid, EPA, may protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma.[4] In addition, animal studies have demonstrated that omega-3 LC PUFAs, such as EPA and DHA, engage in multiple cytoprotective activities that may contribute to antiarrhythmic mechanisms.[5] Arrhythmias are thought to be the cause of "sudden death" in heart disease.

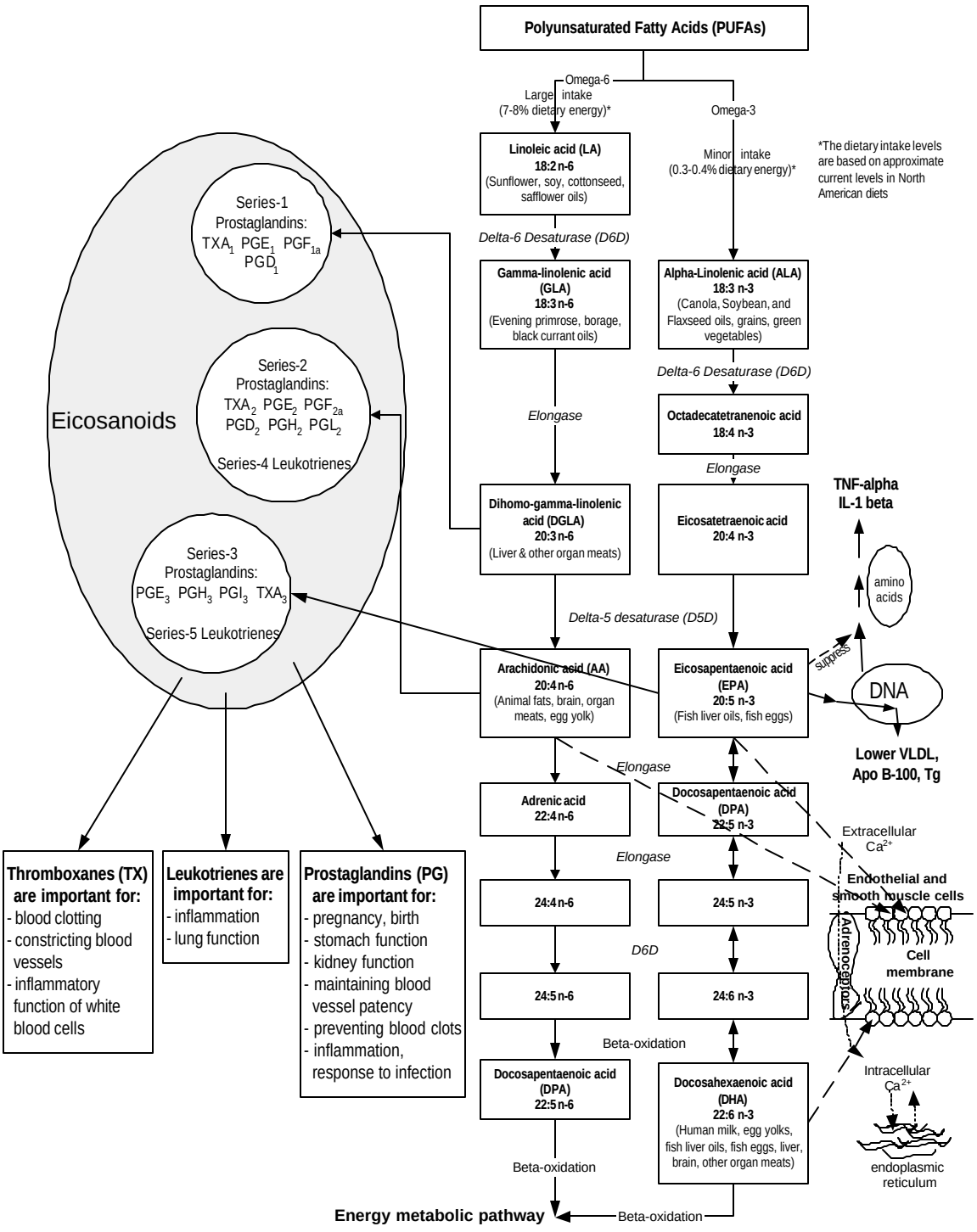
In addition to affecting eicosanoid production as described above, EPA also affects lipoprotein metabolism and decreases the production of other compounds—including cytokines, interleukin 1ß (IL-1ß), and tumor necrosis factor a (TNF-a)—which have pro-inflammatory effects. These compounds exert pro-inflammatory cellular actions that include stimulating the production of collagenase and increasing the expression of adhesion molecules necessary for leukocyte extravasation.[6] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs remains unknown, although suppression of eicosanoid production by omega-3 fatty acids may be involved. EPA can also be converted into the longer chain omega-3 form of docosapentaenoic acid (DPA, 22:5 n-3), and then further elongated and oxygenated into DHA. EPA and DHA are frequently referred to as VLN-3FA—very long chain n-3 fatty acids. DHA, which is thought to be important for brain development and functioning, is present in significant amounts in a variety of food products, including fish, fish liver oils, fish eggs, and organ meats. Similarly, AA can convert into an omega-6 form of DPA.

Studies have reported that omega-3 fatty acids decrease triglycerides (Tg) and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, concomitant with an increase in high density lipoprotein (HDL). However, they appear to increase or have no effect on low density lipoprotein (LDL). Omega-3 fatty acids apparently lower Tg by inhibiting VLDL and apolipoprotein B-100 synthesis, and decreasing post-prandial lipemia.[7] Omega-3 fatty acids, in conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular Tg production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for Tg production.[8]

As noted earlier, omega-6 fatty acids are consumed in larger quantities (> 10 times) than omega-3 fatty acids. Maintaining a sufficient intake of omega-3 fatty acids is particularly

important since many of the body’s physiologic properties depend upon their availability and metabolism.

Figure 1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acids in regulating health/disease markers



U.S. Population Intake of Omega-3 Fatty Acids

The major source of omega-3 fatty acids is dietary intake of fish, fish oil, vegetable oils (principally canola and soybean), some nuts such as walnuts, and, dietary supplements. Two population-based surveys, the third National Health and Nutrition Examination (NHANES III) 1988-94, and the Continuing Survey of Food Intakes by Individuals 1994-98 (CSFII), are the main sources of dietary intake data for the U.S. population. NHANES III collected information on the U.S. population aged =2 months. Mexican Americans and non-Hispanic African-Americans, children =5 years old, and adults = 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall.

The CSFII 1994-96, popularly known as the "What We Eat in America" survey, addressed the requirements of the National Nutrition Monitoring and Related Research Act of 1990 (Public Law 101-445) for continuous monitoring of the dietary status of the American population. The CSFII 1994-96 utilized an improved data-collection method for 24-hour recall known as the multiple-pass approach. Given the large variation in intake from day-to-day, multiple 24-hour recalls are considered to be best suited for most nutrition monitoring and will produce stable estimates of mean nutrient intake from groups of individuals.[9] In 1998, the Supplemental Children's Survey, a survey of food and nutrient intake by children under the age of 10 years, was conducted as a supplement to the CSFII 1994-96. The CSFII 1994-96, 1998 surveyed 20,607 people of all ages with over-sampling of low-income population (<130% of the poverty threshold). Dietary intake data from individuals of all ages were collected over 2 nonconsecutive days via two 1-day dietary recalls.

Table 1 reports the NHANES III survey mean intake ± the standard error of the mean (SEM), in addition to the median and range for each omega-3 fatty acid. Distributions of EPA, DPA, and DHA were very skewed; therefore, the means and standard errors of the means should be used and interpreted with caution. Table 2 reports the CSFII survey mean and median intakes for each omega-3 fatty acid, along with SEMs, as reported in the Dietary Reference Intakes from the Institute of Medicine.[2]

Table 1: Estimates of the mean±standard error of the mean (SEM) intake of linoleic acid (LA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the US population, based on analyses of a single 24-hour dietary recall of NHANES III data

	Grams/day		% Kcal/day	
	Mean±SEM	**Median (range)[1]**	**Mean±SEM**	**Median (range) [1]**
LA (18:2 n-6)	14.1±0.2	9.9 (0 - 168)	5.79±0.05	5.30 (0 - 39.4)
ALA (18:3 n-3)	1.33±0.02	0.90 (0 - 17)	0.55±0.004	0.48 (0 - 4.98)
EPA (20:5 n-3)	0.04±0.003	0.00 (0 - 4.1)	0.02±0.001	0.00 (0 - 0.61)
DHA (22:6 n-3)	0.07±0.004	0.00 (0 - 7.8)	0.03±0.002	0.00 (0 - 2.86)

[1]The distributions are not adjusted for the over-sampling of Mexican-Americans, non-Hispanic African-Americans, children =5 years old, and adults = 60 years old in the NHANES III dataset.

Table 2: Mean, range, median, and standard error of the mean (SEM) of usual daily intakes of linoleic acid (LA), total omega-3 fatty acids (n-3 FA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in the US population, based on CSFII data (1994-1996, 1998)

	Grams/day	
	Mean±SEM	**Median±SEM**
LA (18:2 n-6)	13.0±0.1	12.0±0.1
Total n-3 FA	1.40±0.01	1.30±0.01
ALA (18:3 n-3)	1.30±0.01	1.21±0.01
EPA (20:5 n-3)	0.028	0.004
DPA (22:5 n-3)	0.013	0.005
DHA (22:6 n-3)	0.057±0.018	0.046±0.013

Dietary Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be found in many different sources of food, including fish, shellfish, some nuts, and various plant oils. Selected from the USDA website, Table 3 lists the amount of omega-3 fatty acids in some commonly consumed fish, shellfish, nuts, and edible oils, selected from the USDA website.[10]

Table 3: The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils that contain at least 5 g omega-3 fatty acids per 100 g

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Raw [a])				**Fish, continued**			
Anchovy, European	0.6	0.9	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.2	0.4	0.1	Tuna, Light, Canned in Oil [e]	trace	0.1	trace
Bass, Striped	0.2	0.6	trace	Tuna, Light, Canned in Water [e]	trace	0.2	trace
Bluefish	0.2	0.5	-	Tuna, White, Canned in Oil [e]	trace	0.2	0.2
Carp	0.2	0.1	0.3	Tuna, White, Canned in Water [e]	0.2	0.6	trace
Catfish, Channel	trace	0.2	0.1	Whitefish, Mixed Sp.	0.3	0.9	0.2
Cod, Atlantic	trace	0.1	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	trace	0.1	trace	Wolffish, Atlantic	0.4	0.3	trace
Eel, Mixed Sp.	trace	trace	0.4				
Flounder & Sole Sp.	trace	0.1	trace				
Grouper, Mixed Sp.	trace	0.2	trace	**Shellfish (Raw)**			
Haddock	trace	0.1	trace	Abalone, Mixed Sp.	trace	-	-
Halibut, Atlantic and Pacific	trace	0.3	trace	Clam, Mixed Sp.	trace	trace	trace
Halibut, Greenland	0.5	0.4	trace	Crab, Blue	0.2	0.2	-
Herring, Atlantic	0.7	0.9	0.1	Crayfish, Mixed Sp., Farmed	trace	0.1	trace
Herring, Pacific	1.0	0.7	trace	Lobster, Northern	-	-	-
Mackerel, Atlantic	0.9	1.4	0.2	Mussel, Blue	0.2	0.3	trace
Mackerel, Pacific and Jack	0.6	0.9	trace	Oyster, Eastern, Farmed	0.2	0.2	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Wild	0.3	0.3	trace
Ocean Perch, Atlantic	trace	0.2	trace	Oyster, Pacific	0.4	0.3	trace
Pike, Northern	trace	trace	trace	Scallop, Mixed Sp.	trace	0.1	-
Pike, Walleye	trace	0.2	trace	Shrimp, Mixed Sp.	0.3	0.2	trace
Pollock, Atlantic	trace	0.4	-	Squid, Mixed Sp.	0.1	0.3	trace
Pompano, Florida	0.2	0.4	-				
Roughy, Orange	trace	-	trace				
Salmon, Atlantic, Farmed	0.6	1.3	trace	**Fish Oils**			
Salmon, Atlantic, Wild	0.3	1.1	0.3	Cod Liver Oil	6.9	11.0	0.9
Salmon, Chinook	1.0	0.9	trace	Herring Oil	6.3	4.2	0.8
Salmon, Chinook, Smoked [b]	0.2	0.3	-	Menhaden Oil	13.2	8.6	1.5
Salmon, Chum	0.2	0.4	trace	Salmon Oil	13.0	18.2	1.1
Salmon, Coho, Farmed	0.4	0.8	trace	Sardine Oil	10.1	10.7	1.3
Salmon, Coho, Wild	0.4	0.7	0.2				
Salmon, Pink	0.4	0.6	trace				
Salmon, Pink, Canned [c]	0.9	0.8	trace	**Nuts and Seeds**			
Salmon, Sockeye	0.6	0.7	trace	Butternuts, Dried	-	-	8.7
Sardine, Atlantic, Canned in Oil [d]	0.5	0.5	0.5	Flaxseed			18.1
Seabass, Mixed Sp.	0.2	0.4	-	Walnuts, English	-	-	9.1
Seatrout, Mixed Sp.	0.2	0.2	trace				
Shad, American	1.1	1.3	0.2				
Shark, Mixed Sp.	0.3	0.5	trace	**Plant Oils**			
Snapper, Mixed Sp.	trace	0.3	trace	Canola (Rapeseed)	-	-	9.3
Swordfish	0.1	0.5	0.2	Flaxseed Oil	-	-	53.3
Trout, Mixed Sp.	0.2	0.5	0.2	Soybean Lecithin Oil	-	-	5.1
Trout, Rainbow, Farmed	0.3	0.7	trace	Soybean Oil	-	-	6.8
Trout, Rainbow, Wild	0.2	0.4	0.1	Walnut Oil	-	-	10.4
Tuna, Fresh, Bluefin	0.3	0.9	-	Wheatgerm Oil	-	-	6.9
Tuna, Fresh, Skipjack	trace	0.2	-				

Trace = <0.1; - = 0 or no data; Sp. = species; [a]Except as indicated; [b]Lox.; [c]Solids with bone and liquid; [d]Drained solids with bone; [e]Drained solids.

Asthma: A Chronic Inflammatory Disease

The National Heart, Lung, and Blood Institute (NHLBI) defines asthma as follows:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[11]

Asthmatic episodes are triggered by a variety of stimuli including allergens, environmental irritants, viral infections, exercise or other poorly defined factors.

Burden of Illness

Asthma continues to be a major public health concern for Americans, accounting for an estimated 14.5 million lost workdays for adults and 14 million lost school days in children annually. It is estimated that, annually, this costs the United States $14.0 billion in direct health care costs and indirect costs due to lost productivity.[12] A survey by the National Center for Health Statistics (NHIS) and the Centers for Disease Control and Prevention (CDC) estimated that, in 2001, 20.3 million Americans had asthma (6.3 million children), or 73.4 per 1,000 persons. Children between the ages of 5 and 17 years had the highest prevalence rate with an estimated 98.1 per 1,000 persons, with rates decreasing with age. Females had an approximately 30 percent higher prevalence rate (82.6 per 1,000 persons) than men (63.6 per 1,000 persons); the prevalence rate was 22.7% higher in blacks than in whites. Although there was a decline in asthma prevalence from 1997 to 1999 after a long period of steady increase, rates in 2000 and 2001 indicate a return to the rising trend.[13]

During 2000, 465,000 hospital discharges were due to asthma, with over 43% of discharges in patients under the age of 15. The discharge rate was highest in blacks (32.9 per 10,000). It was estimated that 4,487 people died of asthma in 2000, with black women having the highest mortality rate (4.2 per 100,000[13]).

Asthma Onset and Diagnosis

Asthma most commonly arises in childhood, but may have its onset at any age. For all age groups, the clinical diagnosis of asthma is prompted by the presence of symptoms including wheezing, coughing, episodic breathlessness, and chest tightness. However, identical features are present in many other diseases, confounding the diagnosis of asthma. Episodic wheezing and cough are among the most common symptoms encountered in childhood illnesses, particularly in those under the age of 5.[14] In this age group, the most common cause of asthma-like symptoms is viral respiratory infection;[14] alternative causes of recurrent wheezing include cystic fibrosis, mild recurrent inflammation, primary ciliary dyskinesia syndrome, primary immune deficiency, congenital heart disease, and foreign body aspiration.[15] Wheezing disorders unrelated to these

conditions can also be observed in children under the age of 5 years, and which do not necessarily develop into full-blown asthma later on in life. Further complicating the diagnosis of asthma in this age group is the difficulty in obtaining objective measurements of lung function. Thus, diagnosis is particularly difficult in children under the age of 5, and is based largely on clinical judgment and an assessment of symptoms and clinical findings. Prognostic factors include a family history of asthma or eczema, and the presence of respiratory symptoms (e.g., wheeze).[15]

The longterm prognosis for childhood asthma is quite variable. Although longitudinal studies have reported that asthma in childhood has a good prognosis, most studies do not take into account the severity of childhood symptoms. A longterm follow-up study by The Melbourne Epidemiological Study of Childhood Asthma followed children with asthma through to adolescence and adulthood.[16-20] A classification system based on wheezing frequency, which correlated well with clinical and spirometric features of airway obstruction, was used to assess disease. Results demonstrated that most of the children with persistent asthma had continuing symptoms into adult life, as well as reduced lung function. The amount of wheezing in early adolescence seemed to be a predictor of severity in later life, with 73% of those with few symptoms at 14 continuing to have little or no asthma at 28 years. Similarly, 68% of those with frequent wheezing at 14 still suffered from recurrent asthma at 28 years, and the distribution of severity at age 42 was found not to have changed from that at age 35.[20] Ulrik reported that, although the majority of patients with asthma have a good prognosis, those patients with severe disease are at risk of impaired growth of lung function during childhood and excessive decline in lung function in adulthood.[21]

Recently, a study by Castro-Rodriquez and colleagues reported that a clinical picture of children under the age of 3 years which included persistent wheezing and at least one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis), was strongly predictive of subsequent asthma after the age of six.[22] However, how early symptoms and disease severity predict disease progression into adulthood remains to be determined.

Although asthma most often arises in childhood, the annual incidence of asthma after the age of 20, and for the rest of the lifespan, is estimated to be approximately 100 per 100,000.[23] Adult-onset asthma may be triggered by occupational or environment exposures, respiratory infections, or smoking. Complicating the diagnosis, particularly in older adults, is the existence of other common conditions with asthma-like symptomatology, for example, chronic obstructive pulmonary disease (COPD). COPD is typically associated with a long history of smoking and may have an inflammatory component that is responsive to anti-inflammatory drug intervention, thus blurring the boundary with asthma.[15]

Inflammation in the Pathogenesis of Asthma

Asthma is a chronic inflammatory disease. The inflammatory process is a complex process involving a number of cell types, including mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells.[24] Although the relative contribution of these cells and their mediators varies depending on disease severity, treatment and duration, there are some universal features of the inflammatory response in the airway. In general, upon antigen stimulation, or during acute asthma exacerbations, these cells become activated, releasing mediators that act either directly or indirectly on the airway to perpetuate the asthmatic inflammatory response. Mediators of

inflammation include cytokines and growth factors, as well as the eicosanoids. Chemokines, a large family of small cytokines, are responsible for regulating the trafficking of the leukocytes into the airway.

The inflammatory response can be divided into the early phase response (acute, spasmogenic asthma) and the late phase response (chronic, day-to-day asthma). The acute or early phase inflammatory response occurs immediately upon exposure of a sensitized individual to an allergen or other environmental trigger. The early response is initiated by binding of immunoglobulin E (IgE) antibodies to allergen-specific IgE receptors located predominately on mast cells, macrophages and basophils. Binding signals the cell to release preformed mediators including histamine and tryptase, and newly generated mediators including eicosanoids such as the series-2 prostaglandins (PGE_2) and series-4 leukotrienes. Together, these mediators induce contraction of airway smooth muscle and stimulate afferent nerves, mucus hypersecretion, and vasodilation. The series-2 prostaglandin PGE_2 appears to have a prominent role in the hyperresponsiveness of asthma.

Within hours of the response, activated airway cells release cytokines and chemokines, stimulating the release of inflammatory leukoctyes, especially eosinophils and their precursors. The cytokines include IL-1 to IL-5 along with interferon (IFN)-? and TNF-a. The chemokines act as chemoattractants, regulating the recruitment of inflammatory cells into the airway. Although this recruitment involves virtually all cell types, the allergic response is particularly selective for eosinophils, basophils, and lymphocytes. Eosinophilic infiltration of the airway remains a consistent feature of acute inflammation and is also found in mucosal airway tissue from many patients with chronic persistent asthma.[14] The eosinophils are sources of inflammatory mediators which can injure the airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine release. In addition, the eosinophils can release cysteinyl leukotrienes, such as LTC_4, to contract airway smooth muscle. The T-helper lymphocytes are important in the asthmatic inflammatory response since they are prominent in the airways, and produce high levels of cytokines in response to antigen stimulation or during acute asthma exacerbations.[25] The prostaglandins, particularly PGE_2, modulate the formation of cytokines by T-helper cells. The T-helper cells, particularly the Type 1 T-helper cells, produce IL-2 (IL-2 also causes an increase in TNF) and interferon-gamma, whereas the Type 2 T-helper cells produce the cytokines, IL-4 and IL-5. IL-4 acts to commit B-lymphocytes to the synthesis of IgE. There is also evidence that PGE_2 can act directly on B-lymphocytes, to stimulate the formation of IgE.[26,27] The ability to synthesize IgE antibodies to environmental allergens (i.e., atopy) remains a major risk factor in asthma pathogenesis.[14]

Trends in Asthma Management

The primary goal of asthma management is to control symptoms with minimal adverse effects from pharmacotherapy. In 1997, the NHLBI's National Asthma Education and Prevention Program (NAEPP) convened an expert panel to review the different classes of medications used for the short-term relief or long-term control of asthma symptoms;[11] the report has been recently updated.[14] In brief, the Expert Panel Report 2 concluded that the most effective agents available for longterm control of asthma are those agents that attenuate airway inflammation.[11,14] Since airway inflammation is multifactorial, involving several cell types, cytokines, and mediators, the drugs used to decrease inflammation may act at several different steps in the inflammatory process.[11,14] Agents that modify the asthma process, with some

influencing inflammation, include: beta-2 adrenergic agonists, corticosteroids, leukotriene modifiers, mast-cell stabilizing agents, and theophylline.

The beta-2 adrenergic agonists act by relaxing airway smooth muscle. The so-called "short-acting" beta-2 agonists (e.g., terbutaline, pirbuterol, albuterol) are used to reverse and/or inhibit bronchoconstriction related to an acute asthmatic exacerbation. However, the newer "long-acting" beta-2 agonists (e.g., salmeterol, formoterol) are designed to work as an adjunct to inhaled corticosteroid therapy, providing longterm control of symptoms.

The corticosteroids act by decreasing and preventing bronchial inflammation and airway hyperreactivity. According to the Expert Panel Report 2, corticosteroids are the most potent and effective agents for the longterm control of asthma.[11,14] They are not, however, effective for use in acute asthmatic exacerbations.[11,14]

Leukotriene modifiers comprise two pharmacologic classes of compound: 5-lipooxygenase pathway inhibitors (e.g., zileuton) and leukotriene receptor antagonists (LTRAs: e.g., montelukast, zafirlukast). Only zafirlukast and montelukast are approved for use in children.[14]

The mast-cell stabilizing agents include cromolyn sodium and nedocromil. They inhibit both the early and late phases of bronchoconstriction. These agents interfere with the early and late reaction to allergens by stabilizing mast cell membranes, preventing the release of inflammatory cell mediators, as well as the recruitment and chemotaxis of eosinophils and other inflammatory cells.[11,14] Both agents are recommended as an alternative, but not preferred, medication for the treatment of mild persistent asthma.[14]

Theophylline is a bronchodilating agent used principally as adjuvant therapy in asthma management.[11,14] It is structurally related to caffeine and acts by relaxing smooth muscle in the bronchial airways and in the pulmonary blood vessels. In addition, theophylline has been shown to have immunomodulatory, anti-inflammatory, and bronchoprotective effects.[28,29]

Although early intervention with anti-inflammatory therapy may improve the short-term outcome of asthma, longterm studies are needed to determine if early intervention with anti-inflammatory drugs alters the natural course of the disease, particularly in subjects at high risk for developing asthma.

Asthma and Diet

The recent increase in the incidence of asthma is thought to be due to environmental factors rather than a change in genetic susceptibility.[24] A number of such factors, including air pollution, tobacco smoke, allergen exposure and diet, have been proposed as possible explanations.[30] Although there is a relative abundance of observational and scientific evidence for the link between avoidance of environmental triggers and the reduction in the incidence and severity of asthma, the association between diet, and particularly the consumption of the omega-3 fatty acids, has just recently begun to be studied.[31-33] This interest was sparked in no small part by Horrobin's hypothesis that the low incidence of asthma in Eskimos stems from their consumption of large quantities of oily fish, rich in the omega-3 fatty acids EPA and DHA.[34] Yet, to determine the precise nature of the potentially protective role of omega-3 fatty acid intake in this particular population, alternate or complementary explanations for Horrobin's observations likely require investigation as well (e.g., reduced air pollution and allergen exposure). Finally, research has also focused on evaluating aspects of the biological model suggesting that omega-3 fatty acids' impact on asthma comes from its ability to influence those mediators of inflammation presumed to play a prominent role in the pathogenesis of asthma.